Asian Ethnicity Is a Favorable Prognostic Factor for Overall Survival in Non-small Cell Lung Cancer (NSCLC) and Is Independent of Smoking Status

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Background: We previously showed that Asian ethnicity was an independent favorable prognostic factor in non-small cell lung cancer (NSCLC). Many Asian NSCLC patients were never-smokers, and never-smokers had improved survival than ever-smokers. We investigated whether Asian ethnicity is a favorable prognostic factor independent of smoking status.

Methods: Retrospective population-based study of NSCLC cases from the cancer surveillance programs of three Southern California counties from 1991 to 2005.

Results: A total of 20,140 NSCLC patients with known smoking status were analyzed of which 9.1% were never-smokers and 6.5% were Asians. There was a threefold increase in the percentage of Asian never-smokers as compared with ever-smokers. Asians had the highest overall survival (OS) among the 4 major ethnicities ($p < 0.0001$) and never-smokers had improved OS over ever-smokers ($p = 0.0183$) by univariate analyses. By multivariate analyses, Asian ethnicity was an independent and favorable prognostic factor for OS (versus non-Asian; hazard ratio [HR] = 0.861, 95% confidence interval [CI]: 0.808–0.918, $p < 0.0001$), among smokers (versus non-Asian; HR = 0.867, 95% CI: 0.807–0.931, $p < 0.0001$), and among never-smokers (versus non-Asian; HR = 0.841, 95% CI: 0.728–0.971, $p = 0.0180$). Never-smoker was a favorable prognostic factor if ethnicity was not accounted for (versus ever-smoker; HR = 0.936, 95% CI: 0.886–0.988, $p = 0.0169$) but was no longer an independent favorable prognostic factor (versus ever-smoker; HR = 0.953, 95% CI: 0.902–1.007, $p = 0.0861$) after accounting for ethnicity.

Conclusions: Asian ethnicity is an independent favorable prognostic factor for OS in NSCLC regardless of smoking status.

Key Words: Never-smoker, Prognostic factors, Asian ethnicity, Hispanic ethnicity, epidemiology, Non-small cell lung cancer, California Cancer Registry.

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Lung cancer is the number one cancer cause of death in the world. Most of lung cancer is caused by exposure to tobacco smoke. However, lung cancer in never-smokers constitutes the seventh most common cause of cancer deaths worldwide.[1] Recently lung cancer in never-smokers has been recognized as a different clinical entity with a unique epidemiologic and molecular profiles.[2–5] Lung cancer patients who are never-smokers are predominantly women with adenocarcinoma or bronchioloalveolar carcinoma (BAC) histologies and with younger age at presentation.[2–9] The current published literature is not uniform on whether never-smoking status confers a survival advantage[9] even though the majority of the reports do show that never-smoking status is a favorable prognostic for overall survival (OS) and lung cancer-specific survival.[5–8] In our epidemiologic studies of non-small cell lung cancer (NSCLC) using the statewide California Cancer Registry (CCR) database, we consistently found that Asian ethnicity was an independent favorable prognostic factor for survival by Cox proportional hazards analysis in early stage,[10] advanced stage,[11] or NSCLC as a whole.[12] Given that never-smokers comprised a high proportion of Asian NSCLC patients and that never-smokers tend to have better survival than ever-smokers, we could not definitively conclude the favorable prognostic significance of Asian ethnicity without accounting for smoking status (which was not available in the statewide CCR database). Previously, we had successfully abstracted smoking data from the regional CCR using a text-mining program.[13] In this report, we investigated whether the prognostic significance of Asian ethnicity is independent of smoking status by abstracting smoking status of NSCLC patients from Orange, San Diego, and Imperial counties in Southern California. We further investigated the epidemiologic and survival characteristics of never-smokers with NSCLC from these three counties.

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MATERIALS AND METHODS

Population

This was a retrospective study involving analysis of data from the Cancer Surveillance Programs of Orange, Imperial, and San Diego counties (CSPOC/SANDIOCC databases) in the state of California (area population of 6 million). NSCLC patients diagnosed between 1991 and 2005 with complete follow-up data were included in the study. Tumor site and histology were abstracted as described previously.[13] The histology category of mixed/carcinoma not otherwise specified (NOS)/other was obtained by examining histologic codes that did not further classify NSCLC into adenocarcinoma, squamous cell, large cell, or BAC. American Joint Committee on Cancer (AJCC) stages were determined from programming according to the sixth edition AJCC staging system using available clinical and pathologic tumor, node, metastasis data from the cancer registry. Patient demographic data including ethnicity, gender, surgical techniques, radiation, and chemotherapy given during the first course of therapy and clinicopathologic data such as histologic differentiation were abstracted using Surveillance, Epidemiology, and End Results codes. The measurement of socioeconomic status (SES) and marital status used in this analysis was a composite measure using CCR and census data as described previously.[14]

Smoking status was abstracted by examining individual patient text file using a customized text-mining program.[14] Patients with any documented history of smoking were classified as "ever-smokers." Patients with documentation of no smoking history were classified as "never-smokers." Patients lacking documented information on smoking history were excluded from this analysis. The last date of follow-up was either the date of death or the last date the patient was contacted.

Statistical Analyses

Comparisons of demographic, clinical, and pathologic variables were made for NSCLC patients, using Pearson χ^2 statistic or Fisher exact test for nominal variables and Student *t* test for continuous variables. Comparison of nonparametric values across two groups was done using Wilcoxon rank sum test. Univariate survival rate analyses were estimated using the Kaplan and Meier method, with comparisons made between groups by the log-rank test. Cox proportional hazards modeling using time since diagnosis were performed. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed p value less than 0.05.

Ethical Considerations

This research study was approved by the University of California Irvine Institutional Review Board (IRB #2007-6078).

RESULTS

A total of 20,140 patients with known smoking status were analyzed between 1991 and 2005. One thousand eight hundred thirty-nine patients (9.1%) were never-smokers. The median age of all patients was 69 years (95% confidence level: 49–85). The median follow-up time for all patients was 8 months (range, 0–185). Eight thousand four hundred thirty-four patients with unknown smoking status were excluded from the analysis.

Period of Diagnosis

The proportion of NSCLC patients who were never-smokers steadily increased from periods 1991 to 1995, 1996 to 2000, and 2001 to 2005 (7.8%, 8.8%, and 11.0% respectively, $p_{trend} < 0.0001$). The increase in proportion of never-smokers was significant for both male ($p_{trend} = 0.0018$) and female ($p_{trend} < 0.0001$) patients. The increase in proportion of never-smokers was also significant for Asian (16.7%, 23.9%, and 29.1% respectively, $p_{trend} = 0.0001$) and white ($p_{trend} = 0.0006$) but not for African American ($p_{trend} = 0.2824$) or Hispanic ($p_{trend} = 0.2285$) patients. The percentages of never-smokers among NSCLC patients and for Asian NSCLC patients according to a period of diagnosis were plotted in Figure 1.

Analysis by Smoking Status

Age at Diagnosis

The median age at diagnosis for smokers was 69 years compared with 72 years for never-smokers ($p < 0.0001$; Wilcoxon two-sample test) (Table 1). Nevertheless, the percentage of all never-smokers younger than 50 years was higher than all ever-smokers (9.9% versus 5.2%), for male never-smokers than male ever-smokers (10.3% versus 5.4%), and for female never-smokers versus female ever-smokers (9.7% versus 5.0%).

Gender

A greater proportion of never-smokers were women (65.6%) compared with ever-smokers (43.0% female) ($p < 0.0001$) (Table 1).

Ethnicity

Five Asian subgroups (Filipino, Vietnamese, Japanese, Chinese, and Korean) were made up of the majority (86.1%) of the Asian population. There was about a threefold increase in the percentage of Asians who were never-smokers as compared with ever-smokers. Among female NSCLC patients, there was a twofold increase in Hispanic patients who were never-smokers as compared with ever-smokers and about a sixfold increase in Asian who were never-smokers as compared with ever-smokers.

Histology

There was about a threefold increase in the percentage of BAC among never-smokers (10.6%) compared with ever-smokers (3.3%) whereas there was a corresponding 50% reduction of the percentages of squamous cell carcinoma among ever-smokers (24.6%) compared with never-smokers (10.8%). Adenocarcinoma constituted a greater proportion of histology type from among never-smokers (50.6%) than ever-smokers (39.5%).

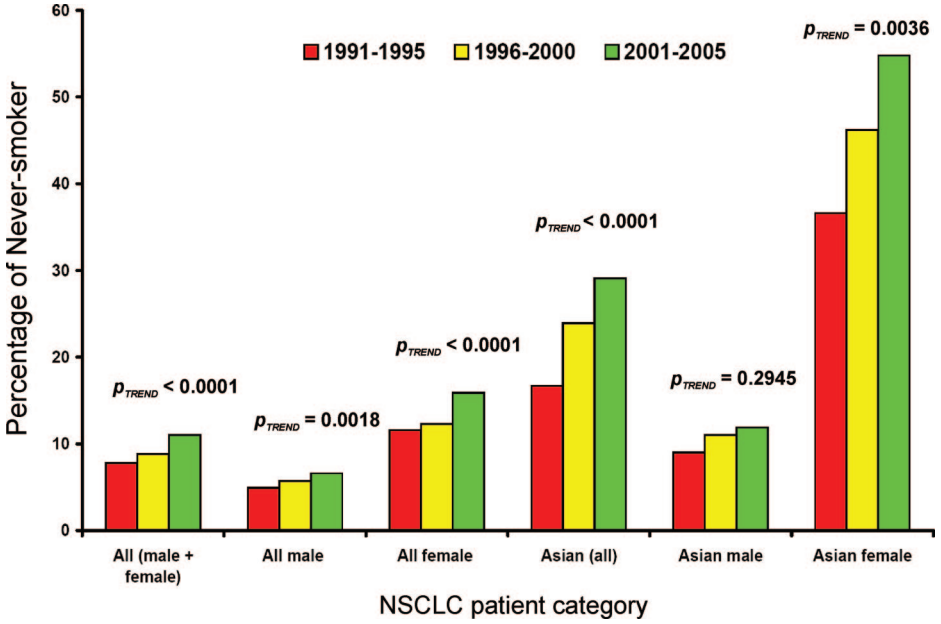

FIGURE 1. Percentages of never-smokers according to periods of diagnosis (1991–1995, 1996–2000, and 2001–2005).

Histologic Differentiation

There was more than twofold increase in the proportion of well-differentiated tumor among never-smokers (9.0%) than ever-smokers (4.0%).

Stage

Slightly more than half of the never-smokers presented with stage 4 disease (50.7%), which was higher than the percentage of stage 4 disease among ever-smokers (45.3%).

Analysis by Ethnicity

NSCLC patients who were never-smokers constituted a much higher proportion of the total NSCLC patients among Asian (24.5%) and Hispanic (14.2%) patients as compared with white (7.6%) and African American (5.4%) patients (Table 2).

Median Age of Diagnosis

White never-smokers had a significant older age of diagnosis than white ever-smokers (74 years versus 70 years; $p < 0.0001$) and so were African American never-smokers (70 years versus 62 years; $p = 0.0216$). Hispanic never-smokers were significantly younger at the time of diagnosis than Hispanic ever-smokers (66 years versus 69 years, $p < 0.0109$). Asian never-smokers were younger than ever-smokers (67 years versus 68 years; $p = 0.1920$) though the difference was not statistically significant.

Gender

Female predominance of never-smokers were evident across all four ethnicities from 62.8% of white, 71.8% of Asian, 72.1% of Hispanic, and 72.7% of African American patients (Table 2). In addition, 48.5% of Asian and 25.8% of Hispanic female NSCLC patients were never-smokers as compared with 10.3% of white and 9.8% of African American female NSCLC patients who were never-smokers (Table 3).

Univariate Survival Analysis

Smoking Status

The 1-year, 2-year, 3-year, 5-year survival estimates and median OS for NSCLC patients who were never-smokers (43.7%, 32.7%, 22.7%, 16.1%, and 11 months, respectively) were significantly better when compared with the survival estimates for ever-smokers (40.0%, 26.1%, 19.9%, 14.2%, and 8 months, respectively; $p = 0.0183$) (Figure 2).

Stage

The 1-year, 5-year survival estimates, and median OS for AJCC stage 1 patients were 81.9%, 47.9%, and 55 months, respectively. The corresponding values were 70.3%, 25.8%, and 24 months, respectively, for stage 2 patients; 39.7%, 8.6%, and 9 months, respectively, for stage 3 patients; and 21.6%, 3.4%, and 4 months, respectively, for stage 4. The difference in survival among the 4 stages was statistically significant ($p < 0.0001$). The survival of patients with unknown stage was intermediate between stage 2 and 3 patients (45.3%, 15.3%, and 11 months, respectively).

Histology

BAC had the most significant and best survival with 1-year, 5- year survival estimates and median OS of 73.3%, 42.7%, and 44 months, respectively. The corresponding values for squamous cell carcinoma were 45.7%, 15.7%, and 11 months, respectively, for large cell carcinoma; 43.0%, 16.3%, and 9 months, respectively, for adenocarcinoma; 31.7%, 11.6%, and 6 months, respectively; and 28.0%, 6.1%, and 5 months, respectively, for mixed/NOS/other histology. The survival difference was statistically different among adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and mixed/NOS/other histologies ($p < 0.0001$).

TABLE 1. Patient Characteristics (Total, Male, and Female) Stratified by Smoking Status

	Total			Male			Female		
	Ever-Smoker	Never-Smoker	*p*	Ever-Smoker	Never-Smoker	*p*	Ever-Smoker	Never-Smoker	*p*
n (%)	18,301 (90.9)	1839 (9.1)		10,431 (94.3)	632 (5.7)		7870 (86.7)	1207 (13.3)	
Median age (yr) (95% CI)	69 (49–84)	72 (44–88)	<0.0001[a]	69 (49–84)	71 (43–88)	0.0033[a]	70 (49–85)	72 (44–88)	<0.0001[a]
Median follow-up time (mo) (range)	8 (0–185)	9 (0–181)	0.2048[a]	7 (0–184)	7 (0–181)	0.3088[a]	9 (0–185)	10 (0–1790	0.5364[a]
Period of diagnosis									
1991–1995	6319 (34.5)	533 (29.0)		3734 (35.8)	193 (30.5)		2585 (32.9)	340 (28.2)	
1996–2000	6202 (33.9)	595 (32.4)		3472 (33.3)	211 (33.4)		2730 (34.7)	384 (31.8)	
2001–2005	5780 (31.6)	711 (38.7)	<0.0001	3225 (30.9)	228 (36.1)	0.0077	2555 (32.5)	483 (40.0)	<0.0001
Age									
0–39	114 (0.6)	51 (2.8)		67 (0.6)	20 (3.2)		47 (0.6)	31 (2.6)	
40–49	842 (4.6)	131 (7.1)		495 (4.8)	45 (7.1)		347 (4.4)	86 (7.1)	
50–59	2735 (14.9)	255 (13.9)		1608 (15.4)	93 (14.7)		1127 (14.3)	162 (13.4)	
60–69	5611 (30.7)	359 (19.5)		3341 (32.0)	132 (20.9)		2270 (28.8)	227 (18.8)	
70–79	6341 (34.7)	568 (30.9)		3512 (33.7)	198 (31.3)		2829 (36.0)	370 (30.7)	
≥80	2658 (14.5)	475 (25.8)	<0.0001	1408 (13.5)	144 (22.8)	<0.0001	1250 (15.9)	331 (27.4)	<0.0001
Sex									
Male	10431 (57.0)	632 (34.4)		—	—		—	—	
Female	7870 (43.0)	1207 (65.6)	<0.0001	—	—		—	—	
Ethnicity									
White	15,418 (84.2)	1270 (69.1)		8465 (81.2)	472 (74.7)		6953 (88.3)	798 (66.1)	
Asian	985 (5.4)	319 (17.3)		742 (7.1)	90 (14.2)		243 (3.1)	229 (19.0)	
Hispanic	1298 (7.1)	215 (11.7)		851 (8.2)	60 (9.5)		447 (5.7)	155 (12.8)	
African-American	578 (3.2)	33 (1.8)		357 (3.4)	9 (1.4)		221 (2.8)	24 (2.0)	
Other/unknown	22 (0.1)	2 (0.1)	<0.0001	16 (0.2)	1 (0.2)	<0.0001	6 (0.08)	1 (0.1)	<0.0001
Socioeconomic status									
SES1 (lowest)	1585 (8.7)	156 (8.5)		1006 (9.6)	53 (8.4)		579 (7.4)	103 (8.5)	
SES2	3098 (16.9)	266 (14.5)		1793 (17.2)	83 (13.1)		1305 (16.6)	183 (15.2)	
SES3	3949 (21.6)	375 (20.4)		2277 (21.8)	115 (18.2)		1672 (21.2)	260 (21.5)	
SES4	4972 (27.2)	476 (25.9)		2782 (26.7)	166 (26.3)		2190 (27.8)	310 (25.7)	
SES5 (highest)	4509 (24.6)	529 (28.8)		2448 (23.5)	200 (31.6)		2061 (26.2)	329 (27.3)	
Unknown	188 (1.0)	37 (2.0)	0.0006	125 (1.2)	15 (2.4)	<0.0001	63 (0.8)	22 (1.8)	0.2496
Marital status									
Married	10,231 (55.9)	1060 (57.6)		6965 (66.8)	458 (72.5)		3266 (41.5)	602 (49.9)	
Unmarried	7700 (42.1)	750 (40.8)		3283 (31.5)	165 (26.1)		4417 (56.1)	585 (48.5)	
Unknown	370 (2.0)	29 (1.6)	0.1988	183 (1.8)	9 (1.4)	0.0125	187 (2.4)	20 (1.7)	<0.0001
Histology									
Adenocarcinoma	7220 (39.5)	930 (50.6)		3885 (37.2)	301 (47.6)		3335 (42.4)	629 (52.1)	
BAC	611 (3.3)	194 (10.6)		272 (2.6)	46 (7.3)		339 (4.3)	148 (12.3)	
Large cell	1341 (7.3)	105 (5.7)		755 (7.2)	39 (6.2)		586 (7.5)	66 (5.5)	
Squamous cell	4510 (24.6)	199 (10.8)		2900 (27.8)	96 (15.2)		1610 (20.5)	103 (8.5)	
Mixed/NOS/Other	4619 (25.2)	411 (22.4)	<0.0001	2619 (25.1)	150 (23.7)	<.0001	2000 (25.4)	261 (21.6)	<0.0001
Histologic differentiation									
Well differentiated	731 (4.0)	165 (9.0)		354 (3.5)	45 (7.1)		367 (4.7)	120 (9.9)	
Moderately differentiated	2719 (14.9)	284 (15.4)		1504 (14.4)	81 (12.8)		1215 (15.4)	203 (16.8)	
Poorly differentiated	6334 (34.6)	458 (24.9)		3632 (34.8)	185 (29.3)		2702 (34.3)	273 (22.6)	
Undifferentiated	1040 (5.7)	62 (3.4)		623 (6.0)	19 (3.0)		417 (5.3)	43 (3.6)	
Unknown	7477 (40.9)	870 (47.3)	<0.0001	4308 (41.3)	302 (47.8)	<0.0001	3169 (40.3)	568 (47.1)	<0.0001
AJCC stage									
Stage 0	4 (0.02)	0 (0.0)		2 (0.02)	0 (0.0)		2 (0.03)	0 (0.0)	
Stage 1	2914 (15.9)	247 (13.4)		1491 (14.3)	66 (10.4)		1423 (18.1)	181 (15.0)	
Stage 2	859 (4.7)	64 (3.5)		483 (4.6)	17 (2.7)		376 (4.8)	47 (3.9)	
Stage 3	3497 (19.1)	271 (14.7)		2071 (19.9)	94 (14.9)		1426 (18.1)	177 (14.7)	
Stage 4	8292 (45.3)	933 (50.7)		4883 (46.8)	360 (57.0)		3409 (43.3)	573 (47.5)	
Unknown	2735 (14.9)	324 (17.6)	<0.0001	1501 (14.4)	95 (15.0)	<0.0001	1234 (15.7)	229 (19.0)	<0.0001
Surgery									
Yes	4932 (27.0)	452 (24.6)		2601 (24.9)	134 (21.2)		2331 (29.6)	318 (26.4)	
No	13345 (72.9)	1382 (75.2)		7811 (74.9)	497 (78.6)		5534 (70.3)	885 (73.3)	
Unknown	24 (0.1)	5 (0.3)	0.0310	19 (0.2)	1 (0.2)	0.1055	5 (0.1)	4 (0.3)	0.0017

(*Continued*)

TABLE 1. (*Continued*)

	Total			Male			Female		
	Ever-Smoker	Never-Smoker	*p*	Ever-Smoker	Never-Smoker	*p*	Ever-Smoker	Never-Smoker	*p*
Radiation									
Yes	7958 (43.5)	655 (35.6)		4799 (46.0)	238 (37.7)		3159 (40.1)	417 (34.6)	
No	10339 (56.5)	1184 (64.4)		5629 (54.0)	394 (62.3)		4710 (59.9)	790 (65.4)	
Unknown	4 (0.02)	0 (0.0)	<0.0001	3 (0.03)	0 (0.0)	0.0002	1 (0.01)	0 (0.0)	0.0010
Chemotherapy									
Yes	5325 (29.1)	624 (33.9)		3160 (30.3)	228 (36.1)		2165 (27.5)	396 (32.8)	
No	12923 (70.6)	1212 (65.9)		7240 (69.4)	404 (63.9)		5683 (72.2)	808 (66.9)	
Unknown	53 (0.3)	3 (0.2)	<0.0001	31 (0.3)	0 (0.0)	0.0041	22 (0.3)	3 (0.3)	0.0007

[a] *p* value calculated by Wilson two-sample test.
NOS, not otherwise specified; CI, confidence interval; SES, socioeconomic status; BAC, bronchioloalveolar carcinoma; AJCC, American Joint Committee on Cancer.

Histologic Differentiation

Well-differentiated histologic grade had the best 1-year, 5-year survival estimates, and median OS (71.8%, 42.1%, and 41 months, respectively) followed by moderately-differentiated tumor (62.8%, 29.1%, and 22 months, respectively), poorly-differentiated tumor (42.2%, 15.3%, and 9 months, respectively), and undifferentiated tumor (33.0%, 11.8%, and 6 months, respectively). Tumor with unknown differentiation had the worst survival (28.2%, 5.6%, and 5 months, respectively). The survival difference was statistically significant ($p < 0.0001$).

Ethnicity

Asian had the best survival among the four ethnicities with 1-year, 5-year survival estimates, and median OS of 43.1%, 13.9%, and 10 months, respectively. The corresponding values for white were 40.5%, 14.7%, and 9 months, respectively; 39.7%, 13.8%, and 8 months, respectively, for African Americans; and 35.6%, 11.3%, and 7 months, respectively, for Hispanics. The survival difference was statistically significant ($p = 0.0001$). We also compared survival of Asians to non-Asians according to AJCC stage. The 1-year, 5-year survival estimates and median OS of stage 1 Asians (86.6%, 53.0%, and 67 months, respectively) were numerically improved and close to statistical significance when compared with stage 1 non-Asians (81.6%, 47.7%, and 54 months, respectively; $p = 0.0614$) (Figure 3*A*). For stage 2 patients, the 1-year, 5-year survival estimates, and median OS of Asians(77.8%, 24.0%, 27 months, respectively) were again numerically improved when compared with non-Asians (69.9%, 25.9%, and 24 months, respectively; $p = 0.6106$) (Figure 3*B*). For stage 3 patients, the 1-year, 5-year survival estimates, and median OS of Asians (46.4%, 11.0%, and 12 months, respectively) were significantly improved when compared with non-Asians (39.2%, 8.4%, and 9 months, respectively; $p = 0.0136$) (Figure 3*C*). For stage 4 patients, the 1-year, 5-year survival estimates, and median OS of Asians (27.7%, 5.0%, and 6 months, respectively) were again significantly improved when compared with non-Asians (21.1%, 3.3%, and 4 months, respectively; $p < 0.0001$) (Figure 3*D*).

Gender

Female patients had significant improved 1-year, 5-year survival estimates, and median OS (44.4%, 17.4%, and 10 months, respectively) as compared with male patients (37.0%, 12.0%, and 7 months, respectively, $p < 0.0001$).

Socioeconomic Status

There was significant improvement in 1-year, 5-year survival estimates, and median OS with increasing SES. The 1-year, 5-year survival estimates, and median OS for the 5 SES quintiles were 36.3%, 11.5%, and 7 months, respectively, for SES1; 35.7%, 11.7%, and 7 months, respectively, for SES2; 38.7%, 13.3%, and 8 months, respectively, for SES3; 41.0%, 15.2%, and 9 months, respectively, for SES4; and 44.7%, 17.1%, and 10 months, respectively, for SES5 ($p < 0.0001$).

Marital Status

Married patients had significant improved 1-year, 5-year survival estimates, and median OS (42.7%, 15.8%, and 9 months, respectively) as compared with unmarried patients (37.3%, 12.6%, and 7 months, respectively, $p < 0.0001$).

Treatment

Among patients with stage 1 disease, surgery conferred significant survival advantage for both never-smokers (median OS: surgery versus no surgery, 89 months versus 17 months, $p < 0.0001$) and ever-smokers (median OS: surgery versus no surgery, 76 months versus 14 months, $p < 0.0001$) and for all four ethnicities (white: 76 months versus 14 months, $p < 0.0001$; Hispanic: 65 months versus 17 months, $p < 0.0001$; Asian: 99 months versus 18 months, $p < 0.0001$; and African American: 100 months versus 15.5 months, $p = 0.0007$). Similarly, radiation conferred significant survival advantage in stage 3 disease for both never-smokers (median OS: radiation versus no radiation, 14 months versus 8 months, $p < 0.0001$) and ever-smokers (median OS: radiation versus no radiation, 11 months versus 5 months, $p < 0.0001$) and among all four ethnicities (white: 11 months versus 5 months, $p < 0.0001$; Hispanic: 11 months versus 6 months, $p = 0.0013$; Asian: 14 months versus 7 months, $p = 0.0850$;

TABLE 2. Patient Characteristics by Ethnicity and Stratified by Smoking Status

	Caucasian (n = 16,688)			Hispanic (n = 1513)			Asian (n = 1304)			African-American (n = 611)		
	Ever-Smoker	Never-Smoker	p	Ever-Smoker	Never-Smoker	p	Ever-Smoker	Never-Smoker	p	Ever-Smoker	Never-Smoker	p
n (%)[a]	15,418 (92.4)	1270 (7.6)		1298 (85.8)	215 (14.2)		985 (75.5)	319 (24.5)		578 (4.6)	33 (5.4)	
Median age (yr) (95% CI)	70 (50–85)	74 (46–89)	<0.0001[b]	69 (46–85)	66 (40–85)	0.0109[b]	68 (46–83)	67 (41–86)	0.1920[b]	62 (43–81)	70 (39–88)	0.0216[b]
Median follow-up time (mo) (range)	8 (0–185)	9 (0–178)	0.5511[b]	6 (0–184)	8 (0–168)	0.0770[b]	8 (0–170)	10 (0–181)	0.2277[b]	7 (0–161)	4 (0–109)	0.4016[b]
Period of diagnosis												
1991–1995	5519 (35.8)	421 (33.2)		378 (29.1)	48 (22.3)		245 (24.9)	49 (15.4)		168 (29.1)	14 (42.4)	
1996–2000	5223 (33.9)	394 (31.0)		418 (32.2	83 (38.6)		351 (35.6)	110 (34.5)		205 (35.5)	8 (24.2)	
2001–2005	4676 (30.3)	455 (35.8)	0.0002	502 (38.7)	84 (39.1)	0.0701	389 (39.5)	160 (50.2)	0.0003	205 (5.5)	11 (33.3)	0.2189
Age												
0–39	72 (0.5)	24 (1.9)		18 (1.4)	10 (4.7)		12 (1.2)	15 (4.7)		12 (2.1)	2 (6.1)	
40–49	622 (4.0)	73 (5.8)		82 (6.3)	26 (12.1)		64 (6.5)	28 (8.8)		74 (12.8)	4 (12.1)	
50–59	2208 (14.2)	153 (12.1)		193 (14.9)	40 (18.6)		172 (17.5)	58 (18.2)		151 (26.1)	4 (12.1)	
60–69	4717 (30.6)	218 (17.2)		394 (30.4)	51 (23.7)		300 (30.5)	85 (26.7)		193 (33.4)	5 (15.2)	
70–79	4352 (35.4)	417 (32.8)		441 (34.0)	58 (27.0)		339 (34.4)	81 (25.4)		106 (18.3)	11 (33.3)	
≥80	2347 (15.2)	385 (30.3)	<0.0001	170 (13.1)	30 (14.0)	<0.0001	98 (10.0)	52 (16.3)	<0.0001	42 (7.3)	7 (21.2)	0.0019
Sex												
Male	8465 (54.9)	472 (37.2)		851 (65.6)	60 (27.9)		742 (75.3)	90 (28.2)		357 (61.8)	9 (27.3)	
Female	6953 (45.1)	798 (62.8)	<0.0001	447 (34.4)	155 (72.1)	<0.0001	243 (24.7)	229 (71.8)	<0.0001	221 (38.2)	24 (72.7)	<0.0001
Socioeconomic status												
SES1 (lowest)	896 (5.8)	45 (3.5)		365 (28.1)	67 (31.2)		122 (12.4)	34 (10.7)		197 (34.1)	10 (30.3)	
SES2	2449 (15.9)	150 (11.8)		280 (21.6)	48 (22.3)		214 (21.7)	63 (19.7)		150 (26.0)	5 (15.2)	
SES3	3331 (21.6)	253 (19.9)		254 (19.6)	44 (20.5)		241 (24.5)	71 (22.3)		118 (20.4)	6 (18.2)	
SES4	4438 (28.8)	373 (29.4)		243 (18.7)	24 (11.2)		216 (21.9)	73 (22.9)		71 (12.3)	6 (18.2)	
SES5 (highest)	4147 (26.9)	424 (33.4)		146 (11.2)	29 (13.5)		176 (17.9)	69 (21.6)		39 (6.7)	6 (18.2)	
Unknown	157 (1.0)	25 (2.0)	<0.0001	10 (0.8)	3 (1.4)	0.1108	14 (1.4)	9 (2.8)	0.4876	3 (0.5)	0 (0.0)	0.0912
Marital status												
Married	8553 (55.5)	712 (56.1)		750 (57.8)	121 (56.3)		724 (73.5)	213 (66.8)		195 (33.7)	14 (42.4)	
Unmarried	6573 (42.6)	542 (42.7)		516 (39.8)	88 (40.9)		236 (24.0)	99 (31.0)		364 (63.0)	19 (57.6)	
Unknown	292 (1.9)	16 (1.3)	0.2685	32 (2.5)	6 (2.8)	0.8985	25 (2.5)	7 (2.2)	0.0422	19 (3.3)	0 (0.0)	0.3831
Histology												
Adenocarcinoma	6069 (39.4)	613 (48.3)		520 (40.1)	111 (51.6)		406 (41.2)	189 (59.3)		221 (38.2)	17 (51.5)	
BAC	522 (3.4)	138 (10.9)		40 (3.1)	23 (10.7)		32 (3.3)	29 (9.1)		16 (2.8)	4 (12.1)	
Large cell	1092 (7.1)	71 (5.6)		132 (10.2)	15 (7.0)		64 (6.5)	17 (5.3)		53 (9.2)	2 (6.1)	
Squamous cell	3840 (24.9)	157 (12.4)		283 (21.8)	18 (8.4)		235 (23.9)	23 (7.2)		144 (24.9)	1 (3.0)	
Mixed/NOS/other	3895 (25.3)	291 (22.9)	<0.0001	323 (24.9)	48 (22.3)	<0.0001	248 (25.2)	61 (19.1)	<0.0001	144 (24.9)	9 (27.3)	0.0025
Histologic differentiation												
Well	638 (4.1)	120 (9.5)		41 (3.2)	20 (9.3)		31 (3.2)	23 (7.2)		21 (3.6)	2 (6.1)	
Moderately	2329 (15.1)	191 (15.0)		168 (12.)	37 (17.2)		137 (13.9)	53 (16.6)		82 (14.2)	3 (9.1)	
Poorly	5382 (34.9)	325 (25.6)		441 (34.0)	43 (30.0)		331 (33.6)	84 (26.3)		177 (30.6)	4 (12.1)	
Undifferentiated	856 (5.6)	49 (3.9)		95 (7.3)	8 (3.7)		49 (5.0)	4 (1.3)		38 (6.6)	1 (3.0)	
Unknown	6213 (40.3)	585 (46.1)	<0.0001	552 (42.6)	107 (49.8)	<0.0001	437 (44.4)	155 (48.6)	<0.0001	260 (45.0)	23 (69.7)	0.0516
AJCC stage												
Stage 0	4 (0.02)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Stage 1	2599 (16.9)	193 (15.2)		140 (10.8)	18 (8.4)		97 (9.9)	34 (10.7)		76 (13.2)	2 (6.1)	
Stage 2	755 (4.9)	55 (4.3)		38 (2.9)	4 (1.9)		41 (4.2)	5 (1.6)		24 (4.2)	0 (0.0)	
Stage 3	2922 (19.0)	193 (15.2)		230 (17.7)	26 (12.1)		231 (23.5)	47 (14.7)		108 (18.7)	5 (15.2)	
Stage 4	6824 (44.3)	587 (46.2)		690 (53.2)	134 (62.3)		475 (48.2)	191 (59.9)		293 (50.7)	19 (57.6)	
Unknown	2314 (15.0)	242 (19.1)	0.0001	200 (15.4)	33 (15.4)	0.0886	141 (14.3)	42 (13.2)	0.0005	77 (13.3)	7 (21.2)	0.3410
Surgery												
Yes	4306 (27.9)	340 (26.8)		265 (20.4)	38 (17.7)		209 (21.2)	69 (21.6)		149 (25.8)	5 (15.2)	
No	11,094 (72.0)	926 (72.9)		1028 (79.2)	176 (81.9)		776 (78.8)	250 (78.4)		428 (74.1)	28 (84.9)	
Unknown	18 (0.1)	4 (0.3)	0.1218	5 (0.4)	1 (0.5)	0.6420	0 (0.0)	0 (0.0)	0.8760	1 (0.2)	0 (0.0)	0.3784
Radiation												
Yes	6682 (43.3)	450 (35.4)		563 (43.4)	79 (36.7)		433 (44.0)	113 (35.4)		268 (46.4)	13 (39.4)	
No	8732 (56.6)	820 (64.6)		735 (56.6)	136 (63.3)		552 (56.0)	206 (64.6)		310 (53.6)	20 (60.6)	
Unknown	4 (0.03)	0 (0.0)	<0.0001	0 (0.0)	0 (0.0)	0.0685	0 (0.0)	0 (0.0)	0.0072	0 (0.0)	0 (0.0)	0.4344
Chemotherapy												
Yes	4375 (28.4)	394 (31.0)		404 (31.1)	78 (36.3)		355 (36.0)	137 (43.0)		183 (31.7)	14 (42.4)	
No	11,001 (71.4)	874 (68.8)		887 (68.3)	136 (63.3)		627 (63.7)	182 (57.1)		394 (68.2)	19 (57.6)	
Unknown	42 (0.3)	2 (0.2)	0.1041	7 (0.5)	1 (0.5)	0.3228	3 (0.3)	0 (0.0)	0.0575	1 (0.2)	0 (0.0)	0.4281

[a] Percentage calculated across the row.
[b] p value calculated by Wilson two-sample test.
NOS, not otherwise specified; CI, confidence interval; SES, socioeconomic status; BAC, bronchioloalveolar carcinoma; AJCC, American Joint Committee on Cancer.

TABLE 3. Breakdown of Smoking Status by Gender and Ethnicity

	Ever-Smoker (%)[a]	Never-Smoker (%)[a]
White		
All (n = 16,688)	15,418 (92.4)	1270 (7.6)
Male (n = 8937)	8465 (94.7)	472 (5.3)
Female (n = 7751)	6953 (89.7)	798 (10.3)
African American		
All (n = 611)	578 (94.6)	33 (5.4)
Male (n = 366)	357 (97.5)	9 (2.5)
Female (n = 245)	221 (90.2)	24 (9.8)
Asian		
All (n = 1304)	985 (75.5)	319 (24.5)
Male (n = 832)	742 (89.2)	90 (10.8)
Female (n = 472)	243 (51.5)	229 (48.5)
Hispanic		
All (n = 1513)	1298 (85.8)	215 (14.2)
Male (n = 911)	851 (93.4)	60 (6.6)
Female (n = 602)	447 (74.3)	155 (25.8)

[a] Percentage calculated across the row.

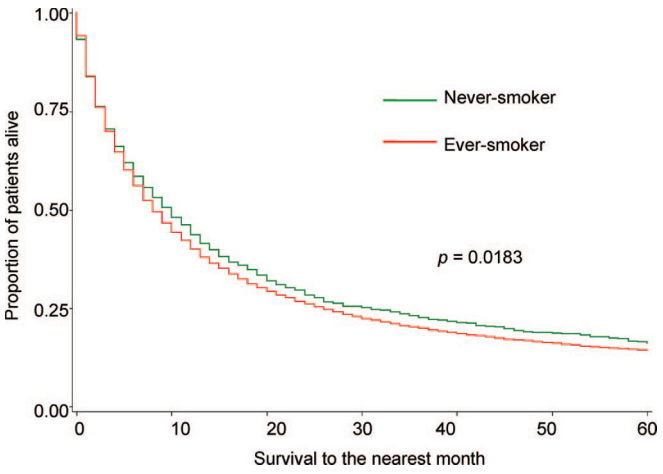

FIGURE 2. Kaplan–Meier survival curves of non-small cell lung cancer (NSCLC) patients according to smoking status.

and African American: 13 months versus 4 months, $p < 0.0001$). For stage 4 disease, chemotherapy also conferred significant survival benefit for both never-smokers (median OS; chemotherapy versus no chemotherapy, 10 months versus 3 months, $p < 0.0001$) and ever-smokers (median OS: chemotherapy versus no chemotherapy, 8 months versus 3 months, $p < 0.0001$) and among all 4 ethnicities (white: 8 months versus 3 months; $p < 0.0001$; Hispanic: 8 months versus 3 months; $p < 0.0001$; Asian: 9 months versus 3 months; $p < 0.0001$; African American: 8 months versus 3 months: $p < 0.0001$). Never-smokers derived an additional 2-month survival benefit as compared with ever-smokers from chemotherapy. Similarly, Asians derived an additional month survival benefit as compared with the other three ethnicities from chemotherapy.

Asian Ethnicity by Smoking Status

Finally, we analyzed survival of Asians according to smoking status. The 1-year, 5-year survival estimates, and median OS of never-smokers (46.0%, 16.2%, and 11 months, respectively) were numerically improved when compared with never-smokers (42.2%, 13.2%, and 9 months, respectively; $p = 0.1001$) (Figure 4).

Multivariate Survival Analysis

Asian ethnicity (versus non-Asian; hazard ratio [HR] = 0.861, 95% confidence interval [CI]: 0.808–0.918, $p < 0.0001$) was an independent and favorable prognostic factor for OS after adjusting for age, gender, smoking status, AJCC stage, histology, histologic differentiation, period of diagnosis, SES, marital status, surgery, radiation, and chemotherapy (Table 4). Other independent favorable prognostic factors were younger age at diagnosis, female gender, early stage of diagnosis, BAC and squamous cell carcinoma histologies, well-differentiated tumor, high SES, being married, diagnosed within the most recent period of diagnosis (2001–2005), and treatment (surgery, radiation, and chemotherapy). Never-smoker was no longer an independent prognostic factor after accounting for ethnicity (Table 4).

Asian ethnicity remained a favorable prognostic factor for OS among never-smokers (versus non-Asian; HR = 0.841, 95% CI: 0.728–0.971, $p = 0.0180$) and among ever-smokers (versus non-Asian; HR = 0.867, 95% CI: 0.807–0.931, $p < 0.0001$) (Table 5).

DISCUSSION

In this study, we demonstrated Asian ethnicity had improved OS in NSCLC when compared with non-Asian ethnicities by a univariate analysis, and Asian ethnicity is an independent favorable prognostic factor for OS in NSCLC by a multivariate analysis after accounting for smoking status and other prognostic factors. It is well established that there is a preponderance of never-smokers among Asian NSCLC patients.[2–4] Never-smokers harbor a high percentage of epidermal growth factor receptor (*EGFR*) mutations and have improved survival outcome. Thus, to investigate the prognostic significance of Asian ethnicity, we abstracted smoking status on 20,140 NSCLC patients to analyze the contribution of smoking status into the Cox model. This allowed us to study the epidemiologic difference between never-smokers and ever-smokers NSCLC patients by gender and ethnicity. We observed the well-characterized features of never-smokers such as female preponderance, increased Asian representation, more adenocarcinoma and BAC, more well-differentiated tumor, more stage 4 disease at presentation, improved treatment survival, and improved survival outcome when compared with ever-smokers. We observed that from 1991 to 2005 there was a statistical significant increase in the proportion of NSCLC patients who were never-smokers, especially among Asian women (Figure 1). In addition, female Asian NSCLC patients had the highest percentage of never-smokers (48.5%) followed by female Hispanic patients (25.8%) (Table 3). Our results are consistent with a report[15] of a higher incidence of female never-smokers with NSCLC from Cali-

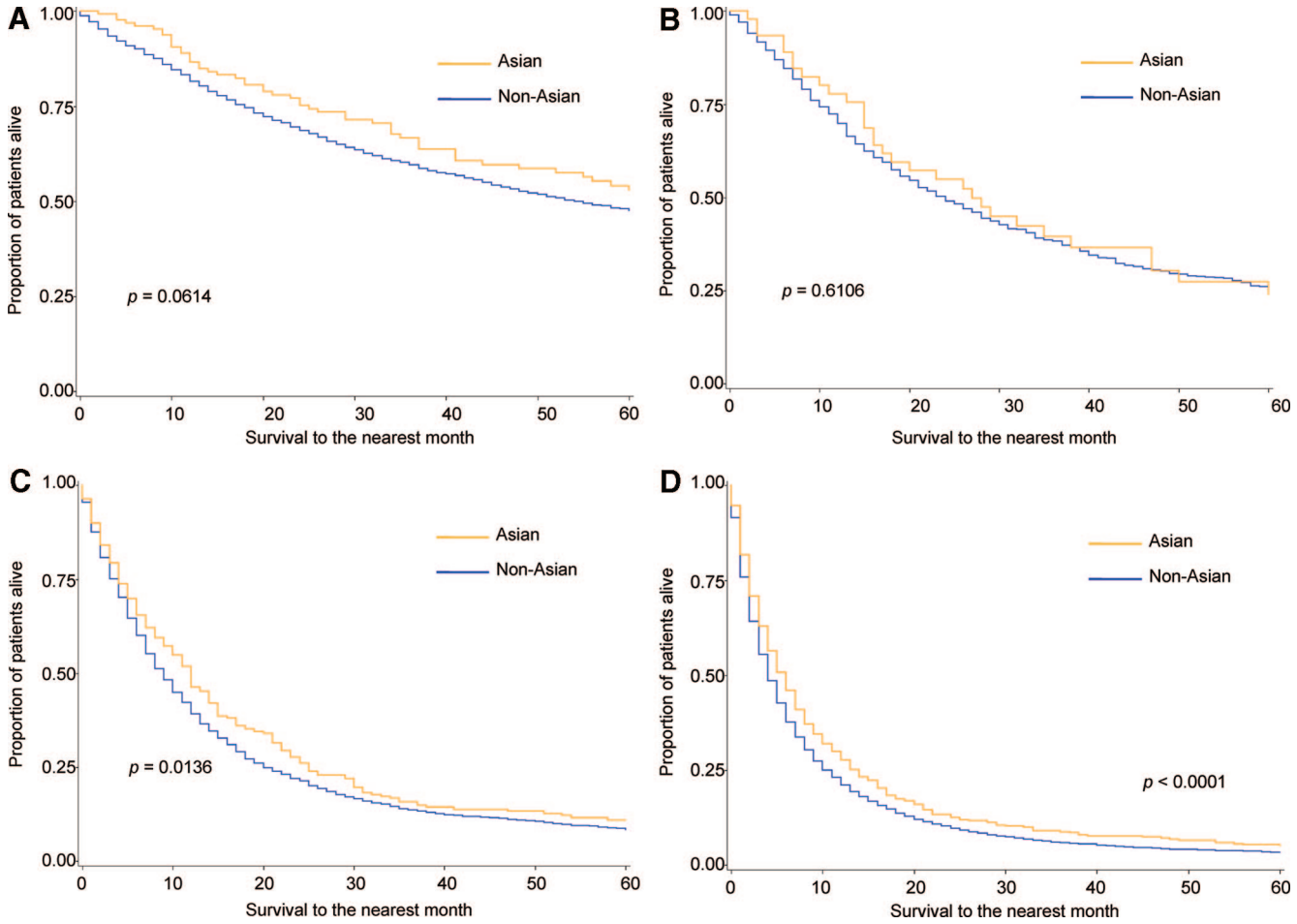

FIGURE 3. *A,* Kaplan–Meier survival curves of stage 1 Asians versus non-Asians. *B,* Kaplan–Meier survival curves of stage 2 Asians versus non-Asians. *C,* Kaplan–Meier survival curves of stage 3 Asians versus non-Asians. *D,* Kaplan–Meier survival curves of stage 4 Asians versus non-Asians.

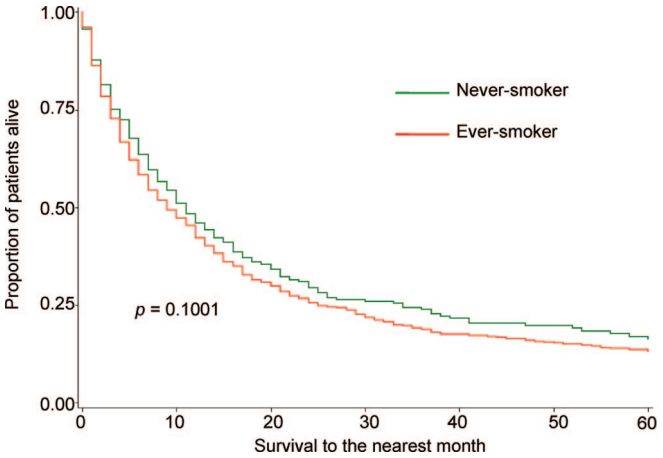

FIGURE 4. Kaplan–Meier survival curves of Asians according to smoking status.

fornia and Hawaii where large Asian and Hispanic populations reside. Of note, only 5.4% of African American NSCLC patients were never-smokers. Consequently, NSCLC in African Americans is a directly tobacco-related disease and demonstrating the importance of smoking cessation efforts in African Americans.

We also observed white[6–9] and African American never-smokers had a higher median age of diagnosis whereas Asian and Hispanic never-smokers had a lower median age of diagnosis when compared with ever-smokers respectively. Green et al reported 54.2% of Mexico-born NSCLC patients aged 40 years and younger were never-smokers with an increase in female-to-male ratio and proportion of adenocarcinoma.[16] Differences in median age of diagnosis among never-smokers from different ethnicities may indicate different pathogenesis.

We demonstrated that Asians had significantly the best OS by univariate analysis and that Asians had improved OS when compared with non-Asians when stratified for stage. Furthermore, among Asians, never-smokers had numeric improved survival than ever-smokers. Our observation that Asian ethnicity is a favorable prognostic factor is in agreement with survival outcomes from recent clinical trials in first-line[17–19] and second line[20–22] treatments of NSCLC in which Asian patients had significantly better median OS than

TABLE 4. Cox Proportional Hazards Model for OS With or Without Ethnicity

	Without Ethnicity			With Ethnicity		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Smoking status						
Ever-smoker	1.000			1.000		
Never-smoker	0.936	0.886–0.988	0.0169	0.953	0.902–1.007	0.0861
Ethnicity						
Non-Asian	—			1.000		
Asian	—	—	—	0.861	0.808–0.918	<0.0001
Gender						
Male	1.000			1.000		
Female	0.848	0.821–0.876	<0.0001	0.845	0.818–0.872	<0.0001
AJCC stage[a]						
1	1.000			1.000		
2	1.693	1.553–1.845	<0.0001	1.694	1.554–1.846	<0.0001
3	2.016	1.891–2.149	<0.0001	2.024	1.899–2.157	<0.0001
4	2.907	2.742–3.082	<0.0001	2.913	2.747–3.088	<0.0001
Age	1.010	1.009–1.012	<0.0001	1.010	1.009–1.012	<0.0001
Histology						
Adenocarcinoma	1.000			1.000		
BAC	0.783	0.711–0.862	<0.0001	0.782	0.710–0.861	<0.0001
Squamous cell carcinoma	0.937	0.901–0.976	0.0016	0.936	0.899–0.974	0.0013
Large cell carcinoma	1.001	0.933–1.075	0.9711	1.000	0.932–1.073	0.9981
Mixed/NOS/other	0.981	0.943–1.021	0.3446	0.980	0.942–1.020	0.3226
Histologic grade[b]						
Well differentiated	1.000			1.000		
Moderately differentiated	1.248	1.135–1.372	<0.0001	1.251	1.137–1.375	<0.0001
Poorly differentiated	1.408	1.286–1.542	<0.0001	1.410	1.287–1.543	<0.0001
Undifferentiated	1.536	1.367–1.725	<0.0001	1.536	1.367–1.725	<0.0001
Period of diagnosis						
1991–1995	1.000			1.000		
1996–2000	0.971	0.937–1.006	0.1077	0.976	0.942–1.011	0.1782
2001–2005	0.907	0.872–0.944	<0.0001	0.912	0.877–0.949	<0.0001
Socioeconomic status	0.987	0.976–0.999	0.0363	0.986	0.974–0.998	0.0189
Marital status[b]						
Married	1.000			1.000		
Unmarried[c]	1.062	1.029–1.097	0.0002	1.056	1.022–1.091	0.0009
Surgery[b]						
No	1.000			1.000		
Yes	0.328	0.312–0.346	<0.0001	0.328	0.311–0.345	<0.0001
Radiation[b]						
No	1.000			1.000		
Yes	0.845	0.818–0.874	<0.0001	0.843	0.816–0.871	<0.0001
Chemotherapy[b]						
No	1.000			1.000		
Yes	0.652	0.628–0.676	<0.0001	0.652	0.628–0.677	<0.0001

[a] Unknown stage included in the Cox proportional hazards analysis but not shown.
[b] Others included in the Cox proportional hazards model analysis but not shown.
[c] Unmarried = single, separated, divorced, and widowed.
OS, overall survival; HR, hazard ratio; CI, confidence interval; BAC, bronchioloalveolar carcinoma; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

white patients independent of treatment assignment. In agreement with our observation, Asian ethnicity was an independent prognostic factor in BR-21 trial after factoring in smoking status.[22] Meta-analysis revealed a high level of EGFR protein portends a poorer outcome in NSCLC.[23] One mechanism that modulates EGFR expression is polymorphism within the *EGFR* gene. Interethnic polymorphism in the EGFR gene that tend to result in lower EGFR expression are more common in Asians compared with other ethnic groups.[24,25] Polymorphism in the *EGFR* gene has also been shown to affect survival in NSCLC[25,26] and may be one of the reasons why Asian ethnicity is a favorable prognostic factor among never-smokers (Table 5).

TABLE 5. Cox Proportional Hazards Model for OS Among Never-Smokers and Ever-Smokers

	Never-Smoker			Ever-Smoker		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Ethnicity						
Non-Asian	1.000			1.000		
Asian	0.841	(0.728–0.971)	0.0180	0.867	(0.807–0.931)	<0.0001
Gender						
Male	1.000			1.000		
Female	0.797	(0.713–0.892)	<0.0001	0.849	(0.821–0.877)	<0.0001
AJCC stage[a]						
1	1.000			1.000		
2	2.462	(1.764–3.438)	<0.0001	1.657	(1.515–1.812)	<0.0001
3	2.210	(1.734–2.816)	<0.0001	2.018	(1.889–2.156)	<0.0001
4	2.993	(2.400–3.731)	<0.0001	2.917	(2.745–3.100)	<0.0001
Age	1.010	(1.006–1.015)	<0.0001	1.010	(1.009–1.012)	<0.0001

Additional variables analyzed in the Cox model: histology, histologic differentiation, period of diagnosis, marital status, socioeconomic status (SES), surgery, radiation, chemotherapy.

[a] Unknown stage included in the Cox proportional hazards model but not shown.

OS, overall survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; SES, socioeconomic status.

One of the major limitations of this study is that we could not capture the degree of environmental tobacco smoke (ETS) exposure. This limitation is not unique to our study as other studies also were not able to quantify the amount of ETS.[5–9] Future investigations should try to capture ETS exposure by detailed questionnaires in both cancer registry and prospective trials and determine which genetic changes in never-smokers with NSCLC are unique to geography and/or ethnicity.

Never-smokers may have better performance status or less comorbidity that we could not capture within the CCR. We reassigned as many patients as possible to one of the 4 AJCC stages to allow more accurate and clinical relevant analysis rather than using the Surveillance, Epidemiology, and End Results summary staging of local, regional and distant disease. Still AJCC stages were unknown in approximately 15% of the patients. Nevertheless, these patients were evenly distributed among ever-smokers and never-smokers, and they were factored in the final Cox analysis. Other limitations included no standardized staging or treatment algorithm. The use of complimentary medicine was also not recorded. Treatment decisions may have been confounded by the physician-patient interaction. The differential benefit of treatment in never-smokers over ever-smokers is retrospective though this observation is supported by recent prospective clinical trials.[17,19,20]

Epidemiologic[2,3,5–9,27] and molecular profiling studies[4,28–30] have clearly demonstrated that NSCLC in never-smokers is distinct from NSCLC in ever-smokers. A recent clinical trial demonstrated that NSCLC in never-smokers is a heterogeneous disease even in a relatively homogeneous Asian population where never-smokers can be broadly divided into patients with *EGFR* wild-type and mutation-positive phenotypes with differential response to chemotherapy or tyrosine kinase inhibitor depending on *EGFR* mutation status.[19] Furthermore, different *EGFR* mutations had different clinical outcomes when treated with the EGFR-tyrosine kinase inhibitor.[31] Future large-scale collaborative epidemiologic and molecular profiling studies should be performed to better characterize ethnic differences of NSCLC in never-smokers and in ever-smokers.

ACKNOWLEDGMENTS

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